SINU-001-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
APPLICATION FOR LETTERS PATENT

INVENTORS:
Albert J. Sinusas
Quing Zhu
Mehran M. Sadeghi

TITLE:
HYBRID OCT/SCINTIGRAPHY INTRAVASCULAR DEVICE

TITLE: HYBRID OCT/SCINTIGRAPHY INTRAVASCULAR DEVICE.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to an imaging device for use within body cavities and/or lumens. More particularly, the invention relates to an imaging device combining OCT with nuclear imaging based scintigraphy to optimize imaging within body cavities and/or lumens.

2. Description of the Prior Art

Coronary artery disease is the major cause of morbidity and mortality in the industrialized world. The major players in this morbidity and mortality are acute coronary syndromes (unstable angina and myocardial infarction), where rupture or erosion of the fibrous cap of a vulnerable atherosclerotic plaque leads to thrombus formation and occlusion of the blood vessel. Despite remarkable progress in treating coronary artery disease, we are still unable to predict which individual patient is prone to develop unstable coronary syndromes. Based on post-mortem studies, vulnerable plaques are morphologically defined as those with high lipid content, a small number of smooth muscle cells, an inflammatory infiltrate and a thin fibrous cap. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G, et al. "Plaque Erosion Is A Major Substrate For Coronary Thrombosis In Acute Myocardial Infarction," Heart, 82:269-72, 1999; P. Libby, "Molecular Bases Of The Acute Coronary Syndromes," Circulation, 91(11): 2844-2850, 1995. There are currently no reliable non-invasive or invasive methods for the detection of these plaques in living subjects.

The arterial wall consists of three layers. Intima, normally only a single cellular layer thick, forms the inner layer surrounding the arterial lumen. It is separated from the middle layer, media, by an internal elastic membrane. In muscular arteries (like coronary arteries), the media mainly consists of smooth muscle cells and extracellular matrix. Adventitia, the outer layer, is separated from the media by an external elastic membrane. As the most common vascular pathologies are associated

with changes in the composition and structure of these layers, there is great interest in high-resolution imaging of the vessel wall. Diagnostic information obtained from such imaging techniques may greatly affect the management of cardiovascular diseases.

Presently, the only widely available diagnostic technique for assessing the vascular wall structure in vivo is intravascular ultrasound. Current clinical applications of imaging the (anatomical) composition of vessel walls include the determination of stenosis in angiographically intermediate lesions, where "lumenography" may not clearly reflect the extent of atherosclerotic burden. Another widely used application of intravascular ultrasound is to determine the accuracy of stent placement after balloon angioplasty.

Despite positive remodeling (increase in external vessel diameter), up to 40% of balloon angioplasties are followed by re-narrowing of arteries (restenosis), which is due to the formation of a thick intimal layer (neointima formation). Neointima formation can be seen in a number of other pathological states, such as diabetic coronary artery disease and chronic graft rejection after cardiac transplantation. Although helpful in the diagnosis of these processes, the usefulness of intravascular ultrasound is limited by its relatively limited resolution. As such, it is often difficult to clearly distinguish between different layers of vascular walls and to clearly demarcate their borders.

In muscular arteries, such as coronary arteries, the intima is relatively echogenic compared to the lumen and media. The trailing edge of intima (that would correspond to the internal elastic membrane) cannot always be distinguished clearly. Media is usually less echogenic than the intima. In some cases the media may appear artifactually thin because of "blooming," an intense reflection from the intima or external elastic membrane. In other cases, the media can appear artifactually thick because of signal attenuation and the weak reflectivity of the internal elastic membrane. In elastic arteries, such as the carotid artery, the media is more echo-reflective because of the higher elastin content. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM,

Yock PG, ACC Clinical Expert Consensus Document On Standards For The Acquisition, Measurement And Reporting Of Intravascular Ultrasound Studies: A Report Of The American College Of Cardiology Task Force On Clinical Expert Consensus Documents (Committee To Develop A Clinical Expert Consensus Document On Standards For Acquisition, Measurement And Reporting Of Intravascular Ultrasound Studies [IVUS]), J Am Coll Cardiol, 37:1478-92, 2001.

Although of some help in defining the anatomy of the plaque, intravascular ultrasound usually lacks the necessary resolution for fine definition of plaque structure. Optical coherent tomography (OCT) can reveal structures within the body to several millimeters in depth with unprecedented resolution on the order of 5 to 15 microns, which is an order of magnitude higher than intravascular ultrasound. D. Huang, E.A. Swanson, C.P. Lin, J.S. Schuman, W.G. Stinson, W. Chang, M.R. Hee, T. Flotte, K. Gregory, C.A. Puliafito, and J.G. Fujimoto, "Optical Coherence Tomography," Science, Vol. 254, 1178-1181, 1991; Rollins A., Sivak M.Jr., Radhakrishnan Sunita, Lass J. H., Huang David, Cooper K. D., Izatt J., "Emerging Clinical Applications Of Optical Coherent Tomogaphy," Optics and Photonics News, 37-41, April 2002; Rashed H, Izatt J, Toth C., "Optical Coherent Tomography Of The Retina," Optics and Photonics News, 48-51, April 2002; M. Brezinski and J. Fujimoto, "Imaging The Cardiovascular System With Optical Coherence Tomography," Optics and Photonics News, 34-35, April 2002; P. Patwari, N. Weissman, S. Boppart, C. Jesser, D. Stamper, J. G. Fujimoto and M. E. Brezinki, "Assessment Of Coronary Plaque With Optical Coherence Tomography And High-Frequency Ultrasound," The American Journal of Cardiology, 85: 641-644, 2000. Recent ex vivo studies have demonstrated that intravascular OCT can differentiate lipids from nonlipids and identify the intimal over the lipid collection. M. Brezinski and J. Fujimoto, "Imaging The Cardiovascular System With Optical Coherence Tomography," Optics and Photonics News, 34-35, April 2002; H. Yabushita, B. Bouma, S. Houser, H. Thomas, I. Jang, K. H. Schlendorf, C. R. Kauffman, M. Shishkov, D. Kang, E. F. Halpern, G. J. Tearney, "Characterization Of Human

Atherosclerosis By Optical Coherence Tomography," Circulation, 106(13): 1640-1653, 2002; IK Jang, BE Bouma, DH Kang, et al, "Visualization Of Coronary Artherosclerotic Plaques In Patients Using Optical Coherent Tomography: Comparison With Intravascular Ultrasound," J. Am. Coll. Cardiol., Vol. 39(4), 604-609, 2002; G. J. Tearney, IK Jang, DH Kang, et al., "Porcine Coronary Imaging In Vivo By Optical Coherent Tomography," ACTA CARDIDL 55(4) 233-237, 2000; J. M. Schmitt, C. L. Petersen, E. Mont and R. Virmani, " Imaging And Characterization Of Coronary Lesions With Optical Coherent Tomography," Proceedings of IEEE International Symposium on Biomedical Imaging, 106-109, Washington D.C. , July 7-10, 2002. High resolution imaging of vessel walls by OCT has, therefore, the potential of opening exciting new directions in the diagnosis and management of coronary artery disease.

As described in U.S. Patent No. 6,445,944, OCT is an interferometric imaging technology. OCT achieves high depth resolution (about 2 μ m to 20 μ m) via a combination of the focal properties of the imaging optics and the coherence properties of the optical source. OCT provides nearly shot-noise-limited detection and thus high sensitivity (>140 dB).

OCT uses the reflected light to obtain a cross-sectional image of tissue adjacent the transparent sheath window. The depth of tissue scan using OCT is based on low coherence interferometry; and the lateral tissue scan is based on the rotation of an optical beam by either a rotating mirror or a mechanical motor. In accordance with a preferred embodiment of the present invention and as those skilled in the art will certainly appreciate, OCT uses an interferometer with reference arm scanning and a low coherence light source.

As such, the light emitted by the OCT system described above is processed in the following manner. First, a low coherence light source is directed onto a beam splitter to produce two beams, a sampling measurement beam and a reference beam.

The sampling beam hits and penetrates the tissue or material to be imaged, and then reflects (backscatters) from the tissue, carrying information about the reflecting points from the surface and the depth of the tissue. The light delivered to the reference arm hits a reference reflector, for example, a mirror or a diffraction grating, and reflects from the

reference reflector. The reference arm travels a given path length, such that the reference reflector either moves or is designed such that the reflection occurs at different distances from the beam splitting point and returns at a different point in time or in space, which actually represents the depth scanning. The amount of such movement represents the desirable depth of penetration of the tissue or object being imaged by the sampling arm. Where OCT is applied the depth of light penetration is typically 2 to 3 millimeters.

The output of the interferometer is the superposition of the electromagnetic fields from the reflected reference arm and the sampling arm reflected from the tissue or material being imaged. When the reflected arms meet, interference is observed only where the path lengths of the reference arm and sampling arm are matched to within the coherence length of the light source. A photodetector detects this interference and converts it into electrical signals. The signals are electronically processed and ultimately displayed, for example, on a computer screen or other monitors.

Each cross-sectional image involves two scans: depth (axial) and width (lateral). Typically, the rate of depth scan is faster than the rate of lateral scan, as 200 to 300 or more depth scans may occur for one lateral scan during live imaging. A typical rate of lateral scanning during live imaging is approximately 26-30 scans per second. A typical OCT probe for linear cross sectional imaging uses a mechanical scanning arrangement in which at least one mechanical part reciprocates to create a scanning motion.

OCT detects reflected light and provides high-resolution imaging of intravascular structures, however, it has limited functional imaging capability. Recent research activities on improving OCT functional imaging capabilities include polarization sensitive OCT, Doppler blood flow OCT, contrast enhanced OCT, spectroscopy OCT, etc. Z. P. Chen, T.E. Milner, S. Srinivas, X.J. Wang, A. Malekafzali, M.J.C. van Germert, and J. S. Nelson, "Noninvasive Imaging Of *In Vivo* Blood Flow Velocity Using Optical Doppler Tomography," Optics Letters, Vol. 22, No. 14, pp. 1119-1121, July, 1997; J.A. Izatt, M.D. Kulkarni, S. Yazdanfar, J.K. Barton and A.J. Welch, "*In Vivo* Bi-Directional Color Doppler Flow Imaging Of Picoliter Blood Volumes Using Optical Coherence Tomography," Optics Letters,

Vol. 22, No. 18, pp. 1439-1441, September, 1997; T.G. van Leeuwen, M.D. Kulkarni, S. Yazdanfar, A.M. Rollins, and J.A. Izatt, "High-Flow-Velocity And Shear-Rate Imaging By Use Of Color Doppler Optical Coherence Tomography," Optics Letters, Vol. 24, No. 22, pp. 1584-1586, November, 1999; DQ. Piao, N. Datta, L. Otis, Q. Zhu, "Quantitative Assessment Of Flow Velocity Estimation Algorithms For Optical Doppler Tomography Imaging," Applied Optics, 41 (29): 6118-6127, 2002; DQ. Piao, L. Otis, and Q. Zhu, "Doppler Angle And Flow Velocity Mapping By Combining Doppler Shift And Doppler Bandwidth Measurements In Optical Doppler Tomography," Optics Letters, in press; F. J-J Toublan, et al, "Magnetically-Induced Optical Contrast Agents For Optical Coherent Tomography," OSA Biomedical Topical Meeting, 257-262, 2002; M. Pierce, B. H. Park, B. Cense and J. F. de Boer, "Simultaneous Intensity, Birefringence, And Flow Measurements With High-Speed Fiber-Based Optical Coherent Tomography," Optics Letters, 27(17) 1534-1536, 2002; C. E. Saxer, J. F. de Bore, B. H. Park, Y. Zhao, Z. Chen and J. S. Nelson, "High-Speed Fiber-Based Polarization-Sensitive Optical Coherent Tomograpy Of In Vivo Human Skin," Optics Letters, 25, 1355-1357,2000; A. Jiao and L. V. Wang, "Two-Dimensional Depth-Resolved Muellaer Matrix Of Biological Tissue Measured With Double-Beam Polarization-Sensitive Optical Coherence Tomography," Optics Letters, Vol. 27 (2), 2002; K. D. Rao, M. A. Choma, S. Yazdanfar, A. Rollins and J. Izatt, "Molecular Contrast In Optical Coherent Tomography By Use Of A Pump-Probe Technique," Optics Letters, Vol. 28, No.28, 341-344, 2003; J. M. Schmitt, S. H. Xiang, and K. M. Yuang, "Differential Absorption Imaging With Optical Coherent Tomography," J. Opt. Soc. Am. A Vol. 15, No.9, 2288-2296, 1998.

Conventional approaches for imaging of atherosclerosis with single photon emission computed tomographic (SPECT) and Positron Emission Tomography (PET), while feasible, provide limited image resolution and/or sensitivity to fully characterize targeted radiolabeled tracers. Therefore, a number of investigators are developing intravascular radiation detection systems for early detection of atherosclerosis. B. E. Patt, J. S. Iwanczyk, L. MacDonald, Y. Yamaguchi, C. Tull,

"Intravascular Probe For Detection Of Vulnerable Plaque," Proceedings of SPIE, Vol. 4508, 88-98, 2001; Lederman RJ. Raylman RR. Fisher SJ. Kison PV. San H. Nabel EG. Wahl RL., "Detection Of Atherosclerosis Using A Novel Positron-Sensitive Probe And 18-Fluorodeoxyglucose (FDG)," Nuclear Medicine Communications. 22(7):747-53, 2001; Raylman RR. Wahl RL, et al., "A Fiber-Optically Coupled Positron-Sensitive Surgical Probe," Journal of Nuclear Medicine, 35(5):909-13, 1994; M. P. Tornai, G. S. Levin, L. R. MacDonald , C. H. Holdsworth E. J. Hoffman, "A Miniature Phoswitch Detector For Gamma-Ray Localization And Beta Imaging," IEEE Transactions on Nuclear Science, 45(3): 1166-1173, 1998; EJ Hoffman, MP Tornai, CS Levin, "Gamma And Beta Intra-Operative Probes," Nucl. Instr. Meth. A389:324:329, 1997.

Nuclear imaging based scintigraphy systems function in the following manner. In practice, injected radioactive agents are targeted to the organ under study. Depending upon the body vessel or cavity being studied, various radioactive agents may be employed so as to produce the highest resolution and signal to background noise image of the vessel or cavity being studied. As those skilled in the art will certainly appreciate, the radiation emitted by the radioactive agents bombards the scintillation fibers, producing a signal (such as light) within the scintillation fibers. The resulting signals are transmitted to the opposite ends of the respective scintillation fibers. The signals are inputted in the signal-receiving elements. The light pulses are then converted into electrical signals and are inputted into a time-to-amplitude converter through constant-fraction discriminators, and a signal delay circuit. The time-to-amplitude converter outputs an electrical pulse to create a pulse height in proportion to the time difference between the time periods required for the light pulses to reach the respective light detectors. The pulse from the time-to-amplitude converter is inputted into the analog-digital converter.

Although more than one radiation can be incident on the scintillation fiber, it is possible to see the incident positions of the radiations by discriminating the pulse-heights of the electrical pulses at the multichannel pulse-height analyzer, and to detect a radiation dose-rate based on count.

Compared with external imaging, intravascular approaches have the significant advantage of detecting localized small lesions that might involve the endothelial cells or the underlying structures. Even an ideal radiolabeled agent for atherosclerosis imaging might deliver only ~0.01% of the administered dose to the target lesion. B. E. Patt, J. S. Iwanczyk, L. MacDonald, Y. Yamaguchi, C. Tull, "Intravascular Probe For Detection Of Vulnerable Plaque," Proceedings of SPIE, Vol. 4508, 88-98, 2001. These intravascular systems offer improved sensitivity for detection of small amounts of radioactivity, although spatial resolution is limited.

While several groups have been developing an intravascular radiation detector, the prior art has so far failed to compensate for intravascular radiation detection devices inability to provide for simultaneous high-resolution imaging of structure. Since most vascular lesions are associated with changes in the composition and structure of the vessel wall, there is great need for such high-resolution imaging of the vessel wall.

Studies have shown that vulnerable plaques are metabolically active and can be detected at an early stage if the endothelium or underlying media is directly interrogated. B. E. Patt, J. S. Iwanczyk, L. MacDonald, Y. Yamaguchi, C. Tull, "Intravascular Probe For Detection Of Vulnerable Plaque," Proceedings of SPIE, Vol. 4508, 88-98, 2001. One of the most effective metabolic tracers in the injured rabbit aorta model employed to screen radiopharmaceuticals is Fluorodeoxyglucose (FDG) labeled with ^{18}F positron (beta) radionuclide emitter. Lederman RJ. Raylman RR. Fisher SJ. Kison PV. San H. Nabel EG. Wahl RL., "Detection Of Atherosclerosis Using A Novel Positron-Sensitive Probe And 18-Fluorodeoxyglucose (FDG)," Nuclear Medicine Communications. 22(7):747-53, 2001. The half-life (110 min) of ^{18}F is relatively long compared to other positron emission tracers. FDG accumulation appears to correspond to regions of subintimal cellular infiltration. FDG uptake is one marker of the relative hypermetabolic state of atherosclerotic tissue, which is characterized by a dense cellular infiltration of macrophages and lymphocytes.

Most catheter-based radiotracer detection systems have focused on beta detection of positron emitting tracers using scintillating plastic fibers. Since the targeted cardiac vessels have diameters of less than 5 mm, they correspond well with the tissue path length (~3 mm) for beta particles with energies of >600 keV. The catheter designed by Patt et al. employs 0.5 mm diameter scintillating fibers. B. E. Patt, J. S. Iwanczyk, L. MacDonald, Y. Yamaguchi, C. Tull, "Intravascular Probe For Detection Of Vulnerable Plaque," Proceedings of SPIE, Vol. 4508, 88-98, 2001. This system has demonstrated acceptable sensitivity for detection of ^{18}F of >400 cps/uCi at 1mm from the detector. ^{18}F labeled tracers have been developed for other targets such as the alpha-v beta-3 integrin, which may be upregulated in the unstable plaque. The detection of the unstable or vulnerable atherosclerotic plaque may be enhanced by more specific vascular markers, like the alpha-v beta-3 integrin. The catheter-based scintillating probes provide limited spatial resolution and can, at most, identify activities about the size of catheter tips (approximately several mms).

With the foregoing in mind, it is apparent a need exists for a system capable of overcoming the individual shortcomings of scintillating probes and OCT. The present invention provides a novel hybrid catheter-based device, which integrates an OCT probe and scintillating fibers for dual-modality high-resolution structural and high-contrast functional imaging of coronary diseases, using ^{18}F labeled tracers. The development of the present device will open an exciting new research direction for high-resolution molecular imaging of vascular, and other intra-cavity diseases.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an imaging device including a delivery device shaped and dimensioned for accessing a predetermined body cavity or lumen, an OCT system linked to the delivery device and a nuclear imaging system linked to the delivery device.

It is also an object of the present invention to provide an imaging device including a control assembly linked to the OCT system and the nuclear imaging system. The control assembly includes processing means adapted for gathering information from the OCT system and the nuclear imaging system and creating imaging information used in the assessment of the body cavity or lumen into which the delivery device is placed.

It is another object of the present invention to provide an imaging device wherein the OCT system includes scanning components housed within the delivery device and an OCT source assembly remote from the delivery device.

It is a further object of the present invention to provide an imaging device wherein the scanning components of the OCT system include an optical fiber extending from the OCT source assembly through the length of the delivery device, a lens secured to a distal end of the optical fiber and a rotating right angle prism positioned for receiving light from the lens.

It is also another object of the present invention to provide an imaging device wherein rotation of the right angle prism is controlled by a motor coupled to the right angle prism.

It is still another object of the present invention to provide an imaging device wherein the motor is housed within a distal end of the delivery device.

It is also an object of the present invention to provide an imaging device wherein the motor is positioned adjacent a proximal end of the delivery device.

It is a further object of the present invention to provide an imaging device wherein the nuclear imaging system includes scintillating fibers positioned adjacent a distal end of the delivery device.

It is another object of the present invention to provide an imaging device wherein the scintillating fibers are sheathed in the area adjacent a proximal end of the delivery device.

It is also an object of the present invention to provide an imaging device wherein two to six scintillating fibers are positioned adjacent the distal end of the delivery device.

It is yet a further object of the present invention to provide an imaging device wherein the scintillating fibers are coupled to a proximal end of the delivery device by optical fibers extending from the scintillating fibers to the proximal end of the delivery device.

It is another object of the present invention to provide a method for imaging body lumens or cavities. The method is achieved by first inserting a delivery device to a predetermined location within a body previously marked with radioactive markers. The delivery device includes an OCT system linked to the delivery device and a nuclear imaging system linked to the delivery device. The method further includes scanning the predetermined location with the OCT system for obtaining a high resolution image and sensing the radioactive markers with the nuclear imaging system to obtain a high contrast image of the predetermined location.

Other objects and advantages of the present invention will become apparent from the following detailed description when viewed in conjunction with the accompanying drawings, which set forth certain embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of the present imaging system.

Figure 2 is a schematic of a first embodiment in accordance with the present invention.

Figure 3 is a schematic of a second embodiment in accordance with the present invention.

Figure 4 is a schematic of the OCT source assembly.

Figure 5 is in vivo simultaneous structural and blood flow imaging of two clusters of the abdominal vessels of a small rat with pulsatile flow.

Figure 6 is a graph of detection sensitivity versus distance between radiation source and scintillating fiber tips.

Figure 7 is a graph of total counts v. lateral position of beta source relative to the scintillating fiber tips.

Figure 8 is an illustration of position sensitive PMT resistor network and multi-channel radiation detection system for spatial mapping.

Figure 9 is a schematic of a prototype in accordance with the present invention.

Figure 10 is a perspective view of the prototype shown in Figure 9.

Figure 11 is co-registered OCT images and positron detection simultaneously acquired from a fresh bovine coronary artery. The location of point source beta emitter is pointed by the white arrow.

Figure 12 is an OCT image showing the layered structure of the vessel of Figure 11.

Figure 13 is a schematic of a recirculation perfusion system.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The detailed embodiments of the present invention are disclosed herein. It should be understood, however, that the disclosed embodiments are merely exemplary of the invention, which may be embodied in various forms. Therefore, the details disclosed herein are not to be interpreted as limiting, but merely as the basis for the claims and as a basis for teaching one skilled in the art how to make and/or use the invention. Where alternate embodiments are described herein, the same reference numerals will be used in designating similar elements.

With reference to the accompanying figures, an imaging device 10 is disclosed. The imaging device is adapted for positioning within a predetermined body lumen and/or cavity and retrieving imaging information relating to the body lumen and/or cavity. The imaging device 10 provides a system capable of offering dual-modality high-resolution structural and high-contrast functional imaging of body lumens and/or cavities In accordance with a preferred embodiment of the present invention, the imaging device 10 is shaped, dimensioned and adapted for intravascular access for obtaining imaging information regarding the detection of unstable atherosclerotic plaque (coronary vessels, carotid vessels, renal vessels, peripheral vessels, etc.), the detection of restenosis following percutaneous angioplasty with or without stenting, the evaluation of brachytherapy following percutaneous angioplasty performed with coated stents or an intravascular radiation source and/or the evaluation of cardiac transplant vasculopathy.

While the present imaging device 10 is adapted for intravascular studies in accordance with a preferred embodiment of the present invention, it is contemplated the present imaging device 10 may be used as an endoscopic device with applications in the evaluation of gastrointestinal pathology. It is further contemplated the present imaging device 10 may be readily modified for use as a bronchoscopic device with applications in the evaluation of pulmonary pathology. It is still further contemplated the present imaging device 10 may be modified for use as an endoscopic device with applications in the detection of tumors in multiple organ systems (for example, gastrointestinal tract, pulmonary tract and/or other organ systems). Where the present imaging device 10 is adapted for other applications it may be linked with laparoscopic surgical techniques and interventions. In particular, the application of the present imaging device 10 to cancer detection will

foster new excitement in the early detection of cancer at the cellular level, which may lead to early detection and final eradication of some deadly diseases.

In accordance with a preferred embodiment of the present invention, and with reference to the alternate embodiments disclosed with reference to Figures 1, 2 and 3, the imaging device 10 includes a delivery device 12 shaped and dimensioned for accessing a predetermined body cavity or lumen. The scanning components 14 of an optical coherent tomography (OCT) system 16 and the sensing components 18 of a nuclear imaging system 20 are housed within the delivery device 12. The imaging device 10 further includes a control assembly 22 linked to the OCT system 16 and the nuclear imaging system 20. The control assembly 22 includes processing means adapted for gathering information from the OCT system 16 and the nuclear imaging system 20 for display on a monitor 24. The control assembly 22 further creates imaging information used in the assessment of the body cavity and/or lumen into which the delivery device 12 is placed.

Optical coherent tomography (OCT) is an imaging technique capable of providing subsurface high-resolution images on the order of 5 to 10 microns, which is an order of magnitude higher than conventional intravascular ultrasound. Nuclear imaging-based intravascular approaches, for example, nuclear imaging based scintigraphy, offer the significant advantage of detecting localized lesions labeled by highly specific radioactive tracers; that is, nuclear imaging approaches offer the ability to provide high contrast imaging of predetermined body vessels. In accordance with the present invention, high-resolution OCT imaging and high-contrast nuclear imaging are integrated for simultaneous structural imaging.

As discussed above, the delivery device 12 is preferably a catheter-based system adapted for intravascular access. As those skilled in the art will certainly appreciate, various catheter structures may be employed without departing from the spirit of the present invention. As will be described below in greater detail, the scanning components 14 of the OCT system 16 and the sensing components 18 of the nuclear imaging system 20 are positioned within the most distal 10-15 mm of the catheter 12. As such, the inclusion of the scanning components 14 of the OCT system 16 and the sensing components 18 of the nuclear imaging system 20 within the catheter 12 does not

substantially affect the flexibility of the catheter 12. The catheter 12 is, therefore, capable of insertion within deep and curved portions of vessels under study.

The catheters 12 utilized in accordance with the present invention must, however, include structural functionality adapted for supporting the scanning components 14 of the OCT system 16 and the nuclear imaging based scintigraphy system 20. In accordance with a preferred embodiment of the present invention, the catheter 12 is constructed with a diameter of approximately 2.0 mm, although those skilled in the art will certainly appreciate various constructions which may be utilized in accordance with the spirit of the present invention.

With reference to the alternate embodiments disclosed in Figures 2 and 3 (the same reference numerals are used for like components), and in accordance with preferred embodiments of the present invention, the scanning components 14 of the OCT system 16 housed within the catheter 12 generally include a single mode optical fiber 26, an ultrasonic micromotor 28 (see Figure 3) or a proximally positioned DC motor 30 (see Figure 2), a gradient index (GRIN) lens 32, a right angle prism 34 directed toward a transparent sheath window 36 formed in the catheter wall 38 and a rotor 40 powered by the ultrasonic micromotor 28 (see Figure 3).

More particularly, the single mode fiber 26 extends from an OCT source assembly 42 through the length of the catheter 12. The GRIN lens 32 is secured to the distal end 44 of the single mode fiber 26. The GRIN lens 32 receives light from the single mode fiber 26 and delivers light intravascularly via the tiny right angle prism 34. The right angle prism 34 is controlled for angular motion by a proximally positioned DC motor 30 (see Figure 2) or by a tiny micrometer 28 (see Figure 3). The light delivered to the prism 34 by the GRIN lens 32 is reflected 90 degrees relative to the longitudinal axis of the catheter 12 at its distal end. The reflected light is passed through the transparent sheath window 36 of the catheter 12 and onto the vascular wall. The prism 34 is then rotated under the control of the motor 28, 30 and the light reflected passes through the transparent sheath window 36 toward the surrounding tissue of the vessel. Since there is no rotation or bending driven by external forces involved in the proximal end of the catheter 12 and the solid part of the catheter is only 10-15 mm in the distal end, the catheter 12 is capable of insertion within deeper and curved vessels.

As shown with reference to Figures 2 and 3, two designs have been contemplated for the implementation of the scanning components of the OCT system 16 in accordance with the present invention. In accordance with a first embodiment, several groups have implemented OCT catheters for intravascular or gastrointestinal structural imaging. Bouma, M.E. Brezenski, N.J. Weissman, J.F. Southern, and J.G. Fujimoto, "Scanning Single-Mode Fiber Optical Catheter-Endoscope For Optical Coherence Tomography," Optics Letters, Vol. 21, No. 7, pp. 543-545, April, 1996; A. M. Rollins, R. Ung-arunyawee, A. Chark, R.C.K. Wong, K. Kobayashi, M.V. Sivak, Jr., and J.A. Izatt, "Real-Time *In Vivo* Imaging Of Human Gastrointestinal Ultrastructure By Use Of Endoscopic Optical Coherence Tomography With A Novel Efficient Interferometer Design," Optics Letters, Vol. 24, No. 19, pp. 1358-1360, October, 1999. Their catheter consists of a DC motor-gear assembly at the proximal end and a rotating shaft. The rotating shaft, which consists of a single-mode optical fiber and distal focusing elements of GRIN lens and right angle prism (or microprism), is driven by the gear assembly and can freely rotate inside the catheter sheath. The bending-induced fiber birefringence as the probe is manipulated within the body is compensated by a faraday rotator at the distal end. A. M. Rollins, R. Ung-arunyawee, A. Chark, R.C.K. Wong, K. Kobayashi, M.V. Sivak, Jr., and J.A. Izatt, "Real-Time *In Vivo* Imaging Of Human Gastrointestinal Ultrastructure By Use Of Endoscopic Optical Coherence Tomography With A Novel Efficient Interferometer Design," Optics Letters, Vol. 24, No. 19, pp. 1358-1360, October, 1999. We contemplate adopting this OCT scanning component design by integrating a single-mode optical fiber 26 and two to eight, preferably two to six, and particularly, four, scintillating fibers 46 inside a catheter 12 (see Figure 2). As will be discussed below in greater detail, the four scintillating fibers 46 improve the sensitivity as well as spatial mapping of radiation activities. Since the single-mode optical fiber 26 connected to the distal GRIN lens 32 and microprism 34 needs to be freely rotated inside the catheter while the scintillating fibers 46 are stationary, an inner sheath or a gap (not shown) is provided between single-mode optical fiber 26 and the scintillating fibers 46 to ensure free rotation of the scanning components 14.

In accordance with a second embodiment, and with reference to Figure 3, a tiny micromotor 28 is positioned at the distal end of the catheter 12. As with the embodiment described

above with reference to Figure 2, the micromotor 28 is coupled to the right angle prism 34 for control rotation. The basic principle of the ultrasonic motor can be found in S.S Lih, Y. Bar-Cohen, and W. Grandia, "Rotary Ultrasonic Motors Actuated By Traveling Flexural Waves," SPIE International Conference, Smart Structures and Materials Symposium, San Diego, CA, 3-6 March 1997. To our knowledge, the ultrasonic micromotors of this size are the smallest that can be made today. This size is small enough to fit into a regular endoscope's catheter.

The proximal end of the catheter 12 has a stationary single-mode fiber 26 and is glued to a GRIN lens 32 of approximately 1 mm in size (in accordance with a preferred embodiment the lens is manufactured by OZ Optics Inc.) for delivering light to a tiny right angle prism 34, which is attached to a rotating ultrasonic micromotor 28 positioned at the distal end of the catheter. The light delivered to the prism is reflected 90 degrees and focused inside the tissue. The speed of the smallest motors can go up to 2000 ~3000 rpm, which corresponds to more than 25 rotations per second. Since one rotation of the micromotor generates one frame of a B-scan OCT image, we can at least achieve 25 frames per second based on current available motor specifications.

This design does not require an inner sheath as is required with the first embodiment, because both optical fiber 26 and scintillating fibers 46 are stationary. However, the catheter sheath 38 must provide a rigid housing for the motor 28 since the micromotor 28 is positioned at the distal end. This is achieved by the provision of motor terminators 48. In addition, the GRIN lens 32, although separated from the motor assembly 28, must be housed rigidly as well to maintain stable light alignment and focusing.

The catheter 12 is made with biocompatible material, such as fused silica. In order to maintain a desired housing for the motor 28 and GRIN lens 32 while providing a transparent sheath window 36 to beta particle and OCT light, a rigid transparent plastic capillary tubing less than 10mm in length is positioned at the catheter 12 tip, and the micromotor assembly 28 plus GRIN lens 32 are glued inside the plastic capillary tubing 36 with optical cement.

In practice, the present OCT system 16 functions in the following manner. Light is applied to the single mode fiber 26. The transmitted light is passed through the GRIN lens 32 secured to the distal end 44 of the single mode fiber 26 and the light is ultimately delivered intravascularly via

the tiny right angle prism 34. The right angle prism 34 is controlled for angular motion by the micromotor 28 or the proximally positioned DC motor 30. The light delivered to the prism 34 by the GRIN lens 32 is reflected 90 degrees relative to the longitudinal axis of the catheter 12 at its distal end. The reflected light is passed through the transparent sheath window 36 of the catheter 12 and onto the vascular wall. The right angle prism 34 is then rotated under the control of the motor 28, 30 and the light reflected passes through the transparent sheath window 36 toward the surrounding tissue of the vessel. The light is then reflected back to the OCT system 16 and ultimately utilized in the creation of an image of the scanned vessel.

As such, and as those skilled in will appreciate, the light emitted by the OCT system 16 described above is processed in the following manner. First, a low coherence light source is directed onto a beam splitter to produce two beams, a sampling measurement beam and a reference beam. The sampling arm and the reference arm are then transmitted through the single mode fiber 26, the gradient index lens 32 and the right angle prism 34 where they are applied to the vessel tissue.

The sampling arm hits and penetrates the tissue or material to be imaged, and then reflects (backscatters) from the tissue, carrying information about the reflecting points from the surface and the depth of the tissue. The reference arm hits a reference reflector, for example, a mirror or a diffraction grating, and reflects from the reference reflector. The reference arm travels a given path length, such that the reference reflector either moves or is designed such that the reflection occurs at different distances from the beam splitting point and returns at a different point in time or in space, which actually represents the depth scanning. The amount of such movement represents the desirable depth of penetration of the tissue or object being imaged by the sampling beam. Where OCT is applied the depth of light penetration is typically 2 to 3 millimeters.

The output of the interferometer is the superposition of the electromagnetic fields from the reflected reference arm and the sampling arm reflected from the tissue or material being imaged. The output is gathered by the right angle prism 34 and transmitted through the single mode fiber 26 to the control assembly 22 where the information is processed to produce an image for viewing. When the reflected arms meet, interference is observed only where the path lengths of the reference arm and sampling arm are matched to within the coherence length of the light source. A

photodetector detects this interference and converts it into electrical signals. The signals are electronically processed and ultimately displayed, for example, on a computer screen or other monitor.

In accordance with a preferred embodiment of the present invention, the reference arm, sampling arm and reflected beams are generated and processed in the following manner. More particularly, and in accordance with a preferred embodiment of the present invention, two OCT source assemblies 42 have been developed for utilization in conjunction with the OCT system of the present invention. As those skilled in the art will certainly appreciate, the OCT source assembly 42 is positioned remote from the scanning components 14 and is linked to the scanning components 14 via the single mode fiber 26 described above. The respective source assemblies 42 are described in DQ. Piao, L. Otis, and Q. Zhu, "Doppler Angle And Flow Velocity Mapping By Combining Doppler Shift And Doppler Bandwidth Measurements In Optical Doppler Tomography," Optics Letters, (28) No.13., 1120-1123; Chen, NG and Zhu, Q, "Rotary Mirror Array for High Speed Optical Coherence Tomography," Optics Letters, (27) No.8., 607-609, April, 2002, which are incorporated herein by reference (copies attached hereto). In addition to the OCT source assemblies 42, a DSP real-time data processing unit, which can be used in conjunction with the present vascular imaging system, is also provided. In accordance with a preferred embodiment of the present invention, a DSP real-time data processing unit is disclosed in Yan, S., Piao, DQ, Chen Y., and Zhu Q, "A DSP-Based Real-Time Optical Doppler Tomography System," J. of BioOptics, submitted May, 2003, which is incorporated herein by reference (copy attached hereto).

In accordance with a preferred embodiment of the present invention, and with reference to Figure 4, the OCT source assembly 42 is a typical balanced setup configured with one 1×2 and one 2×2 fiber couplers 50, 52. The low coherence source is a superluminescent diode 54 with approximately 1310nm center wavelength, 60nm spectral width, and 10.0mW maximum output power. In the reference arm, a scanning optical delay line based on Littrow-mounting of diffraction grating 56 is used to generate range scanning and a phase modulation for carrier frequency as well. In the sample arm, a galvanometer 58 and achromatic lens pair 60, 61 are integrated to perform

repeatable lateral scanning, which is essential for the demonstration of continuous monitoring of structure imaging and blood flow.

In the detection arm, reflected light is transmitted through a glass capillary 74, a lens 76, 77 and galvanometer 72. The signal is detected differentially by an auto-dual balanced receiver 62, with which the source intensity noise is rejected. The signal is then amplified, bandpass filtered 64 and digitized using a computer 70. Using this system, one frame cross-sectional imaging per second is obtained by driving reference arm and sample arm galvanometers with approximately a 128 Hz triangle wave and a 1Hz saw tooth wave, respectively.

The imaging frame rate of an OCT source assembly 42 employing grating-based delay line is set by the galvanometer 72. For a frame rate of 8 frames/second, the galvanometer scanning speed is $f_g = 2048Hz$ assuming 256 A-lines per frame. At this scanning speed, the phase modulation is in the mega-hertz range. To facilitate this high speed scanning, a photo-receiver and filter having a broad bandwidth are needed. In accordance with a preferred embodiment of the grating-based OCT source assembly described above, the photo-receiver has a cutoff frequency of 125KHz, and the band-pass filter has maximum bandwidth of 102.4KHz. Limited by these two components, the current delay line cannot run at higher than 128Hz. As such, it is contemplated that the current photo-receiver and filter may be replaced with Newfocus 1817-FC photo-receiver and Frequency Devices 818 series filters to achieve 8 frames/second imaging frame rate.

With regard to the DSP real-time data processing unit and display unit, they provide for simultaneous tissue structure and blood flow imaging based on a custom designed digital signal processor (DSP) module. Yan, S., Piao, DQ, Chen Y., and Zhu Q, "A DSP-based real-time optical Doppler tomography system," J. of BioOptics, submitted May. 2003. The DSP is incorporated into the above-described OCT source assembly. Two advanced velocity estimation algorithms are embedded in this DSP module. Experiments on intralipid flow demonstrate that this DSP system is capable of imaging pulsatile flow at a rate of several hundred pulses per minute. *In vivo* real-time imaging capability of pulsatile blood flow in small rate is also demonstrated (see Figure 5).

In addition, and in accordance with a further embodiment of the OCT source assembly 42, a fast OCT source assembly 42 is provided for implementing a periodical modulation of the optical

path length in the reference arm. As mentioned above, this embodiment is disclosed in Chen, NG and Zhu, Q, "Rotary Mirror Array For High Speed Optical Coherence Tomography," Optics Letters, (27) No.8, 607-609, April, 2002, which is incorporated herein by reference. The fast OCT source assembly includes a linear delay line. The OCT source assembly 42 uses a regular motor of 4000 revolutions per minute (rpm). Up to 2400 A-lines were acquired every second in a 2 mm range, with less than 0.1% nonlinear effects. For a typical B-scan consisting of 256 A-scan lines, 8 frames/second have been achieved. A much higher scan rate up to 30 frames/second can be readily obtained by replacing our current motor with high-speed motors, e.g., 24,000-30,000 rpm.

As discussed above, nuclear imaging is combined with OCT in an effort to negate the deficiencies inherent in the use of OCT. In accordance with a preferred embodiment of the present invention, and with Reference to Figures 2 and 3, nuclear imaging is achieved through the utilization of scintillating fibers 46. However, it is contemplated other nuclear imaging techniques may be employed without departing from the spirit of the present invention.

In accordance with a preferred embodiment, the present imaging device 10 includes a plurality of scintillating fibers (four in accordance with a preferred embodiment of the present invention) distributed around an OCT single mode fiber 26 positioned in the center of the catheter 12. Four scintillating fibers 46 improve the sensitivity as well as spatial mapping of radiation activities. The four scintillating fibers 46 are approximately 0.5 mm in size and are designed to provide a coarse spatial resolution regarding the approximate size of detected radiation inside the vessel in which the present imaging device is utilized.

As those skilled in the art will certainly appreciate, scintillating fibers 46 of approximately 0.5 mm have been chosen in accordance with a preferred embodiment of the present invention and other sizes may be utilized depending upon required functionality without departing from the spirit of the present invention. In addition, four scintillating fibers 46 are employed in accordance with a preferred embodiment of the present invention, although two to eight fiber versions have been contemplated and those skilled in the art may certainly appreciate other fiber arrangements improving the positron detection sensitivity and spatial mapping without departing from the spirit of the present invention.

The scintillating fibers 46 extend the entire length of the catheter 12 and are ultimately connected to the control assembly 22 for transmission of the signal generated by radiation emitted within the body vessel or cavity. In order to accommodate the need for flexibility required by the present imaging device 10, the present invention employs the approach described in B. E. Patt, J. S. Iwanczyk, L. MacDonald, Y. Yamaguchi, C. Tull, "Intravascular probe for detection of vulnerable plaque," Proceedings of SPIE, Vol. 4508, 88-98, 2001, by fusing a regular optical fibers 45 with a scintillating fiber tip 47. The regular optical fiber 45 will be used for light delivery and the scintillating fiber tip 47 of several millimeters in length will be used for beta particle detection at the catheter tip. As those skilled in the art will certainly appreciate, there is a trade off between the length of the scintillating fiber tip 47 and the sensitivity of the positron detection. As such, those skilled in the art will appreciate that the length of the fibers may be varied without departing from the spirit of the present invention.

With regard to the scintillating fibers 46, the scintillating fibers 46 are very similar to conventional optical fibers except that they are doped with scintillating phosphors (1 ~2%) in the core. In accordance with a preferred embodiment, standard plastic scintillating fiber 46 from Bicron (Model # BCF-12) of 0.5 mm in outer diameter and 1.5 m in length are used. These fibers 46 have been used in testing to evaluate the sensitivity of the fiber and signal-to-noise ratio of the nuclear imaging data acquisition system. We have used sealed Ti-24 beta sources for the reported studies and the Ti-24 beta (765 keV β^-) source has very similar spectrum as ^{18}F (635 keV β^+). B. E. Patt, J. S. Iwanczyk, L. MacDonald, Y. Yamaguchi, C. Tull, "Intravascular Probe For Detection Of Vulnerable Plaque," Proceedings of SPIE, Vol. 4508, 88-98, 2001. Beta rays have a mean free path length of approximately 3mm before they interact with low-Z plastic scintillation detectors. The high-energy beta particles >600 keV trapped by the scintillating fibers 46 result in thousands of photons in the visible region (peak at 440nm), which produce a short light pulse. The plastic scintillator exhibits very fast luminescent-decay time (~3ns) and requires interface with a fast high-gain photomultiplier tube (PMT) 78 that is capable of resolving the first photoelectrons of a light pulse produced by the scintillator.

Since the detection sensitivity of the scintillating highly depends on the distance of the source to the scintillating fiber tip 47 and the number of scintillating fibers 46 used, we have evaluated the sensitivity of the present system by translating the source with a linear stage away from the scintillating fiber tips 47. The scintillating fibers 46 were grouped as 1, 2, 4, 6, respectively. Figure 6 shows that the sensitivity increases as the number of scintillating fibers 46 is increased and the sensitivity decreases as the fiber tip 47 to source distance is reduced.

Another parameter trade-off related to the hybrid catheter design is the sensitivity vs. resolution. To provide a higher spatial resolution for radiation detection, the scintillating fiber 46 length exposed to the radiation should be small. However, smaller scintillating fiber length will reduce the detection sensitivity. We have evaluated this trade-off by exposing the scintillating fiber tip 47 of 2 mm, 4mm, and 6 mm to the 1 uCi beta source and recording the total counts when the source was translated laterally. Six scintillating fibers were used for this test. Figure 7 shows the testing results which suggest that exposing fiber tip 47 of 6 mm to the radiation will reduce resolution by half but double the sensitivity.

To provide a higher spatial resolution for radiation detection, the scintillating fibers 46 at the proximal end to the catheter 12 tip region must be shielded from radiation, for example, with a sheath 49. In our prototype (described below) with a single scintillating fiber 46, a 6 mm scintillating fiber tip 47 was exposed to the beta source and the rest of the fiber was shielded with glass tubing 80.

In accordance with a preferred embodiment of the present invention, a 2x2 multianode photon multiplier tubes (PMT) 78 (R5900U-00-M4, Hamamatsu) is employed for detecting optical signals from the four scintillating optical fibers 46. This PMT 78 is very compact, about 30 mm by 30 mm by 24 mm in three dimensions and only 26 grams in weight. Its spectral response ranges from 300 to 650 nm with a peak at 420 nm, which is appropriate for this application. It features high-speed response and low cross talk. The typical value for anode pulse rise time is 1.2 ns, and the full width at half maximum of transit time spread is only 0.32 ns. The cross talk between different channels is generally less than 4%. The internal gain of R5900 is typically $5X10^5$, while the anode dark current per channel is about 0.5 nA (after 30 minutes storage in darkness).

Position sensitive PMT 78 is read out by a resistor divider chain producing +X, -X, +Y and -Y positions signals. Each of the signals will need to be preamplified, shaped with a linear amplifier and then converted from analog to digital. We will use four electronic channels connected to X_A, X_B, Y_C, Y_D outputs from the position sensitive PMT 78 (see Figure 8) to record the spectrum of each signal and the outputs will be weighted based on $(X\ Y) = (X_A/(X_A+X_B), Y_A/(Y_A+Y_B))$ to produce an approximate spatial map of the detected radiation activity. The spatial map will be displayed as hot spots. B. E. Patt, J. S. Iwanczyk, L. MacDonald, Y. Yamaguchi, C. Tull, "Intravascular Probe For Detection Of Vulnerable Plaque," Proceedings of SPIE, Vol. 4508, 88-98, 2001.

Attention is directed to possible optical cross-talk between scintillating fibers 46. Bicron scintillating fibers 46 are sealed well with the extramural absorber to minimize optical cross-talk. Residual cross-talk is measured by selectively transmitting light to each fiber 46 and measuring the outputs from the rest. If further sealing is needed, absorbing chambers will be added between scintillating fibers 46. The optical cross-talk between OCT fiber 26 and scintillating fiber 46 is readily removed by optical filter because the wavelength of the superluminescent diode source 54 of OCT is 1.3 μm, which is well above the emission peak (435 nm) of scintillating fibers 46.

As briefly discussed above, a control assembly 22 combines the OCT system 16 and a nuclear imaging based scintigraphy system 20 to creating a highly functional imaging system. In particular, the control assembly 22 includes 1) synchronization of OCT system and nuclear imaging system on data acquisition, 2) co-registration of OCT and nuclear imaging display, 3) use of a high-resolution OCT image to guide the high sensitivity nuclear imaging at suspicious vessel sections seen by OCT or use of high sensitivity nuclear imaging to guide the high-resolution OCT at suspicious vessel sections detected by nuclear imaging.

To demonstrate the feasibility of a combined OCT and radiation detection with co-registered position information, a prototype imaging device 10 was constructed and is shown in Figures 9 and 10. In this prototype, a GRIN lens 32 of 2.5mm outside diameter is placed inside a 3mmx3mm square glass tubing 80, and a 0.5mm scintillating fiber 46 is attached to the GRIN lens and positioned in one corner of the square tubing 80. The light from GRIN lens 32 is reflected 90°

by a tiny mirror, or prism, 34 attached to a rotation stage 81 through a shaft 82. The shaft 82 is also placed inside another piece of 3mm×3mm square glass tubing 84. The two glass tubings 80, 84 holding the GRIN lens 32 and the 90° reflection mirror 34 are aligned and separated about 10mm, in which space the 6 mm scintillating fiber 46 tip is exposed to air to avoid attenuation of beta radiation by the glass tubing 80, 84. The rotation stage 81 is driven by a DC motor 86 through a timing belt-pulley assembly, and the speed of the stage rotation can be controlled. It should be appreciated the motor 86 and the assembly are too big for an intravascular catheter and the embodiments described above disclosed designs for the implementation of the present imaging device for *in vivo* usage. Since OCT A-line scanning speed is configured to be 64Hz, 512 A-lines are obtained in one revolution of the 90° reflection mirror, and the OCT signal is processed to have circumferential display corresponding to the cross-section of the blood vessel.

To demonstrate the simultaneous OCT structural imaging and radiation detection, we have acquired co-registered OCT and radiation data from freshly excised pieces of bovine coronary arteries. For the convenient of experiments, the examined artery is translated in 2mm steps, and an OCT across-section image and radiation counts are acquired simultaneously at each step. The beta source is positioned closer to a hole left at the artery and translated with the artery. Figures 11 and 12 show the co-registration result. When the beta source reaches the scintillating fiber 46 detection range, the total photon counting is increased significantly. When the beta source is away from the detection range of the fiber 46, the total photon counting reduces to background level. The spatial resolution of the radiation detection is poor because a 6 mm single scintillating fiber tip 47 was exposed to the beta source. The resolution can be improved by exposing smaller fiber tip 47 to the source as discussed before. Nevertheless, the feasibility of co-registration can be readily demonstrated from this result.

We plan to study light attenuation issues using the recirculation perfusion system shown in Figure 13. The perfusion loop consists of a peristaltic pump 88, a 1×2 flow switch 90, a damper 92, a perfusion guide 94 through the blood vessel 96 and biocompatible plastic tubing 98. When the perfusion is through the damper 92, a continuous flow will be applied; when the perfusion is

bypassing the damper 92, a pulsatile flow will be generated by the peristaltic pump 88. The perfusion rate is controlled by changing the speed of pump. This perfusion system allows for the infusion of buffer (phosphate buffer saline) in the absence and presence of simulated pulsatile flow, with or without porcine red blood cells. Based on our experience in OCT blood flow studies, diluted blood to a quarter of its concentration will not cause significant light attenuation for the vessel size of less than 1 millimeter in diameter. We will further test our catheter-based OCT system with different concentrations of red blood cells. The OCT catheter will be advanced and images will be taken within an intact pig vascular segment (2 cm in length), which is interfaced with the recirculating system. The buffer with different amounts of red blood cells will be perfused within the recirculation system. The OCT image quality will be analyzed and results obtained will answer questions for future *in vivo* studies in larger animal models regarding how often and how much saline is needed for the flushing. The agents that have been reported to enhance the light penetration to 120-150% include glucose, dextrans, propylene glycol and trazograph. V. Tuchin, X. Xu, and R. K. Wang, "Dynamic Optical Coherence Tomography In Studies Of Optical Clearing, Sedimentation, And Aggregation Of Immersed Blood," Applied Optics, Vol 41(1): 258:271, 2002. We will study glucose and dextrans in conjunction with saline flush in an attempt to find whether saline flush can be avoided or not. If saline flush is required, we will find the optimal amount of saline water in the presence of each of the agents.

For sensitive detection of beta activities, the background gamma radiation needs to be estimated and subtracted. For *in vivo* beta imaging, circulating blood will contain certain amount of beta and gamma activities and the total count rate will be the summation of both activities, which will contaminate the actual count rates measured at the lesion locations. We will use the recirculation system shown in Figure 13 to assess the background gamma activities in the absence and presence of circulating blood that carries certain amount of radioactive agents. To evaluate spatial resolution within the arterial wall various amounts of ^{18}F (from 1 nCi to 1 uCi) in 10 microliters of solvent will be injected into the arterial wall. The exact amount injected into the vessel wall will be calculated by measuring the activity left in the syringe. The catheter will be advanced back and forth and detected counts will be registered. The profile of the activity versus location will

be plotted, and the full width at half maximum of the activity profile will be determined. Similar analyses will be performed for different scintillating fiber thickness and numbers in the catheter for different amounts of radioactivity. In addition to localization along the artery, we will evaluate the circumferential spatial resolution for multifiber catheter designs. The trade-off between the spatial resolution (related to the length of the scintillating fiber tip) and the sensitivity of radiation detection will be evaluated. In addition, the data acquisition time needed to obtain total counts with high activity vs background ratio will be evaluated. The same piece of artery may be used for several evaluations depending on the spatial resolution. To evaluate the system in the presence of higher levels of background activity these experiments will be repeated in the absence and presence of different amount of circulating ^{18}F and background radiation will be estimated for each level of activity. We will also take advantage of the relative short half-life of ^{18}F to evaluate the count sensitivity of the system.

Induction of experimental atherosclerosis in rabbits will be employed in testing the efficacy of the present imaging device as further development proceeds. Specifically, New Zealand White (NZW) rabbits (4-5 mon old) weighing 2.5 to 3.0 kg will be fed a 0.5% cholesterol diet custom mixed in 6% peanut oil; the non-injured control animals will be fed normal rabbit chow. One week following initiation of the high-fat diet, anesthetized rabbits will undergo deendothelialization of the infra-diaphragmatic aorta with a 4F Fogarty embolectomy catheter passed via right femoral artery. Rabbits will be continued on the hyperlipidemic diet for 4 months. NZW rabbit is large enough to allow in vivo testing of the proposed hybrid intravascular OCT/scintillator catheter.

Rabbits will be injected intravenously with ^{18}Fdeoxyglucose (FDG), and the hybrid intravascular OCT/scintillator catheter will be placed in the aorta for imaging under fluoroscopic guidance. We anticipate optimal uptake in the aorta approximately 30 mins after radiotracer injection. Serial blood samples will be drawn for evaluation of blood clearance of the radiotracer. Rabbits will be euthanized after in vivo imaging. The injured segment of the aorta will then be placed on our perfusion apparatus for ex vivo imaging. Following ex vivo imaging, the entire length of the aorta will be exposed and cleaned of adherent adventitial fat and connective tissue and removed for ex vivo analysis. The entire aorta will then be segmented into 2 mm pieces. These

segments will be weighed and counted in an automatic well-type gamma counter for determination of the percent injected dose per gram tissue (%ID/g) of the radiolabeled ligands. The aortic specimens will then be submitted for histopathological studies.

Pathological characterization of the aortic atherosclerotic lesions will be undertaken by histological assessment and immunohistochemical evaluation of the constituents of neointimal layer. Histochemical staining will also be performed for determining the distribution of macrophages, and the presence of apoptosis of macrophages. Prevalence of macrophages will be correlated between %ID/gram uptake of ^{18}Fdeoxyglucose.

We will evaluate the hybrid OCT/scintigraphy device for *ex vivo* analysis of vascular structure and function in normal (n = 6) and atherosclerotic (n = 6) NZW rabbit aorta, comparing imaging results with postmortem histology and tissue counting. In the final phase of testing, we will establish the feasibility of *in vivo* imaging with the Hybrid OCT/ scintigraphy intravascular catheter in normal (n = 6) and abnormal atherosclerotic rabbit aorta (n = 6). As previously outlined, NZW rabbits on hyperlipidemic diet with endothelial injury will be utilized for a subset of the *ex vivo* and *in vivo* studies. The *in vivo* images will be directly compared with images acquired from the same rabbit aortas mounted on our *ex vivo* testing system. This initial testing will establish resolution of the OCT system under true conditions of pulsatile flow in the presence of circulating blood. We anticipate that the catheter system will require incorporating a flushing system immediately proximal to the active imaging component of the catheter. In the rabbit model, the flushing will be initially accomplished with a long sheath placed in the aorta via the carotid with the aid of a guide wire. After the guide catheter is positioned, the guide wire will be withdrawn, and the hybrid catheter will be advanced through the guide catheter with the imaging component just distal to the guide catheter. The OCT images and the radiation counts will be acquired while flushing between the OCT catheter and blood vessel is periodically conducted. However, a flushing system ultimately will need to be integrated with the catheter.

A total of 24 rabbits will be utilized over a two year period, recognizing approximately a 25% loss rate. Initial testing of the hybrid OCT/ scintigraphy catheter will be performed on porcine coronary vascular tissue, however, subsequent *ex vivo* testing will be performed on NZW rabbits.

Final testing of intravascular anatomic and functional FDG imaging will be conducted in atherosclerotic NZW rabbits as outlined above.

While the preferred embodiments have been shown and described, it will be understood that there is no intent to limit the invention by such disclosure, but rather, is intended to cover all modifications and alternate constructions falling within the spirit and scope of the invention as defined in the appended claims.

CLAIMS

1. An imaging device, comprising:

a delivery device shaped and dimensioned for accessing a predetermined body cavity or lumen;

an OCT system linked to the delivery device; and

a nuclear imaging system linked to the delivery device.

2. The imaging device according to claim 1, further including a control assembly linked to the OCT system and the nuclear imaging system, the control assembly includes processing means adapted for gathering information from the OCT system and the nuclear imaging system and creating imaging information used in the assessment of the body cavity or lumen into which the delivery device is placed.

3. The imaging device according to claim 1, wherein the OCT system includes scanning components housed within the delivery device and an OCT source assembly remote from the delivery device.

4. The imaging device according to claim 3, wherein the scanning components of the OCT system include an optical fiber extending from the OCT source assembly through the length of the catheter, a lens secured to a distal end of the optical fiber and a rotating right angle prism positioned for receiving light from the lens.

5. The imaging device according to claim 4, wherein rotation of the right angle prism is controlled by a motor coupled to the right angle prism.

6. The imaging device according to claim 5, wherein the motor is housed within a distal end of the delivery device.

7. The imaging device according to claim 5, wherein the motor is positioned adjacent a proximal end of the delivery device.

8. The imaging device according to claim 1, wherein the nuclear imaging system includes scintillating fibers positioned adjacent a distal end of the delivery device.

9. The imaging device according to claim 8, wherein the scintillating fibers are sheathed in the area adjacent a proximal end of the delivery device.

10. The imaging device according to claim 8, wherein two to six scintillating fibers are positioned adjacent the distal end of the delivery device and are adapted for determining the radial position of a radiation source.

11. The imaging device according to claim 8, wherein the scintillating fibers are coupled to a proximal end of the delivery device by optical fibers extending from the scintillating fibers to the proximal end of the delivery device.

12. A method for imaging body lumens or cavities, comprising the following steps:

inserting a delivery device to a predetermined location within a body previously marked with radioactive markers, the delivery device including an OCT system linked to the delivery device and a nuclear imaging system linked to the delivery device;

scanning the predetermined location with the OCT system for obtaining a high resolution image and sensing the radioactive markers with the nuclear imaging system to obtain a high contrast image of the predetermined location.

13. The method according to claim 12, further including the step of processing information from the OCT system and the nuclear imaging system and creating imaging information used in the assessment of the body cavity or lumen into which the delivery device is placed.

14. The method according to claim 12, wherein the predetermined location is vessels of the cardiac system.

15. The method according to claim 12, wherein the predetermined location is chosen from the group consisting of the cardiac system, the gastrointestinal system and the pulmonary system.

16. The method according to claim 12, wherein the nuclear imaging system includes at least one scintillating fiber positioned adjacent a distal end of the delivery device.

17. The method according to claim 16, wherein the scintillating fiber is sheathed in the area adjacent a proximal end of the delivery device.

18. The method according to claim 16, wherein two to six scintillating fibers are positioned adjacent the distal end of the delivery device and are adapted for determining the radial position of a radiation source.

19. The method according to claim 16, wherein the scintillating fiber is coupled to a proximal end of the delivery device by an optical fiber extending from the scintillating fiber to the proximal end of the delivery device.

ABSTRACT OF THE DISCLOSURE

An imaging device includes a delivery device shaped and dimensioned for accessing a predetermined body cavity or lumen, an OCT system linked to the delivery device and a nuclear imaging system linked to the delivery device. The imaging device further includes a control assembly linked to the OCT system and the nuclear imaging system. The control assembly includes processing means adapted for gathering information from the OCT system and the nuclear imaging system and creating imaging information used in the assessment of the body cavity or lumen into which the delivery device is placed.